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REMARKS

Claims 30-45, 57 and 58 were pending prior to the present amendment. Claims 30-45, 57 and 58 have been cancelled.

Claim 59 has been added to claim a method of subjecting a sample to rapid thermal cycling. Support is found throughout and specifically, for example, at page 23, lines 7-21, Claim 30 and figures 5, 9A and 9C of the present specification as originally filed. This claim is also supported throughout and specifically, for example, at page 15, line 14 to page 16, line 7 and claims 19 and 20 of U.S. Application Serial No. 07/534,029 (the '029 application) as originally filed.

Claim 60 has been added as a Claim depending from Claim 59, specifying repetition of the steps. Support is found, for example, in Claim 30 of the present specification and page 15, lines 14-16 of the '029 application.

Claim 61 has been added as a claim depending from Claim 59 or 60, specifying a plurality of sample holders. Support is found, for example, at page 6, lines 8-10 of the present specification and at page 8, lines 5-10 of the '029 application.

Claim 62 has been added as a claim depending from Claim 59 or 60, specifying the first predetermined period of time. Support is found, for example, in figures 5 and 6 of both the present specification and the '029 application.

Claim 63 has been added as a claim depending from Claim 59 or 60, specifying the first predetermined period of time. Support is found, for example, in figures 5 and 6 of both the present specification and the '029 application.

Claim 64 has been added as a claim depending from Claim 59 or 60, specifying an aspect of the lowering in step b). Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 65 has been added as a claim depending from Claim 59 or 60, specifying an aspect of the lowering in step b). Support is found, for example, in figure 7 of both the present specification and the '029 application.

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Claim 66 has been added as a claim depending from Claim 59 or 60, specifying an aspect of the lowering in step b). Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 67 has been added as a claim depending from Claim 59 or 60, specifying the difference between the first and second temperatures. Support is found, for example, at page 24, lines 18-21 and in figure 7 of the present specification and at page 17, lines 1-4 and figure 7 of the '029 application.

Claim 68 has been added as a claim depending from Claim 59 or 60, specifying the second predetermined period. Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 69 has been added as a claim depending from Claim 59 or 60, specifying the second predetermined period. Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 70 has been added to claim a method of amplifying nucleic acid. Support is found throughout and specifically, for example, at page 23, lines 7-21, Claim 30 and figures 5, 9A and 9C of the present specification as originally filed. This claim is also supported throughout and specifically, for example, at page 15, line 14 to page 16, line 7 and claims 19 and 20 of the '029 application.

Claim 71 has been added as a Claim depending from Claim 70, specifying inclusion of a nucleic acid polymerizing enzyme in the sample. Support is found, for example, at page 13, lines 17-20, page 23, lines 9-14 and in Claim 30 of the present specification and at page 7, lines 13-16 and page 15, lines 16-21 of the '029 application.

Claim 72 has been added as a claim depending from Claim 70, specifying a plurality of sample holders. Support is found, for example, at page 6, lines 8-10 of the present specification and at page 8, lines 5-10 of the '029 application.

Claim 73 has been added as a claim depending from Claim 70, specifying the first predetermined period of time. Support is found, for example, in figures 5 and 6 of both the present specification and the '029 application.

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Claim 74 has been added as a claim depending from Claim 70, specifying an aspect of the lowering in step b). Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 75 has been added as a claim depending from Claim 74, specifying an aspect of the lowering in step b). Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 76 has been added as a claim depending from Claim 70, specifying an aspect of the lowering in step b). Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 77 has been added as a claim depending from Claim 70, specifying an aspect of the lowering in step b). Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 78 has been added as a claim depending from Claim 70, specifying the difference between the first and second temperatures. Support is found, for example, at page 24, lines 18-21 and in figure 7 of the present specification and at page 17, lines 1-4 and figure 7 of the '029 application.

Claim 79 has been added as a claim depending from Claim 70, specifying the second predetermined period. Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 80 has been added as a claim depending from Claim 79, specifying the second predetermined period. Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 81 has been added to claim a method of subjecting a sample to rapid thermal cycling. Support is found, for example, at page 20, line 9 to page 21 line 14 and in figure 7 of the present specification and at page 13, line 5 to page 14, line 5 and in figure 7 of the '029 application.

Claim 82 has been added as a claim depending from Claim 81, providing for an additional temperature raising. Support is found throughout and specifically, for example, at page 23, lines 7-21, Claim 30 and figures 5, 9A and 9C of the present specification as originally filed. This claim is also supported throughout and specifically, for example, at

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page 15, line 14 to page 16, line 7 and claims 19 and 20 of U.S. Application Serial No. 07/534,029 (the '029 application) as originally filed.

Claim 83 has been added as a Claim depending from Claim 81 or 82, specifying repetition of the steps. Support is found, for example, in original Claim 23 of the present specification and in original Claim 17 of the '029 application.

Claim 84 has been added as a claim depending from Claim 81 or 82, specifying an aspect of the lowering in step b). Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 85 has been added as a claim depending from Claim 81 or 82, specifying the difference between the first and second temperatures. Support is found, for example, at page 24, lines 18-21 and in figure 7 of the present specification and at page 17, lines 1-4 and figure 7 of the '029 application.

Claim 86 has been added as a claim depending from Claim 81 or 82, specifying the first predetermined period of time. Support is found, for example, in figure 6 of both the present specification and the '029 application.

Claim 87 has been added as a claim depending from Claim 81 or 82, specifying the first predetermined period of time. Support is found, for example, in figure 6 of both the present specification and the '029 application.

Claim 88 has been added as a claim depending from Claim 81 or 82, specifying the second predetermined period. Support is found, for example, in figure 7 of both the present specification and the '029 application.

Claim 89 has been added as a claim depending from Claim 81 or 82, specifying the second predetermined period. Support is found, for example, in figure 7 of both the present specification and the '029 application.

Applicants submit that the present amendments introduce no new matter.

The following remarks are directed to the Office Action dated May 24, 2000 (Paper No. 12; hereinafter, Office Action). Although the Office Action is written with regard to now-cancelled claims, certain points are relevant to the present set of claims and Applicants would like to address these points as a preface for examination of the present claims.

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Priority of the Claimed Invention

The Office Action cited several aspects of the prior claims which were suggested to not be supported by the priority parent applications. Applicants respectfully traverse this conclusion.

While not necessarily agreeing with the conclusion, Applicants have written the present claims so that they are unambiguously supported by even the earliest priority application, namely U.S. Application Serial No. 07/534,029 (the '029 application).

The Office Action Cited the term "sample holding structure" as lacking written basis in the priority documents. The present claims recite a "sample holder containing a sample".

The Examiner's attention is directed to page 2, lines 9-10, wherein the specification describes the invention as relating to "a thermal cyclers which can be used to cycle sample containers". Further discussion of the enablement of the presently claimed methods reciting such a sample holder can be found below. Applicants submit that the present wording is supported in the present application as well as all of the priority documents.

The phrase "at least 15°C higher" with regard to one of the increasing temperature changes was cited as not being supported by the priority documents. This phrase is not found in the present claims.

The phrases "10 to 90 seconds" and "10 to 60 seconds" with regard to the cycle durations was cited in the Office Action as not being supported in the priority documents. The present claims recite the phrase "30-60 seconds" with regard to the completion of the several steps of the claimed methods, which is literally supported in the '029 application at page 16, lines 4-7.

Finally, utilization of a "heated fluid" is cited as not being supported in the priority documents. The Examiner's attention is directed to page 14, lines 6-10 and page 20, lines 1-4 of the '029 application, wherein the application teaches the use of fluids other than air in the presently claimed methods.

In light of the discussion above, Applicants submit that the claims are fully supported by all of the priority applications, including the '029 application.

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Rejections under 35 U.S.C. § 112, first paragraph

Claims 30-45 and 57 were rejected under 35 U.S.C. § 112, first paragraph as not being enabled by the specification. Applicants respectfully traverse in so far as the rejection might pertain to the present claims..

The test of enablement is whether, at the time of filing, the specification provides sufficient information for one of ordinary skill in the art to practice the claimed invention without undue experimentation. The satisfaction of the enablement requirement should consider at least the factors of: a) breadth of the claims; b) nature of the invention; c) state of the prior art; d) level of skill of the ordinary artisan; e) level of predictability in the art; f) amount of direction provided by the inventors; g) the existence of working examples; and h) the quantity of experimentation need to make or use the invention based on the content of the specification (*In re Wands* 858 F.2d 731, 735, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988; MPEP § 2164.01(a)). Applicants submit that the disclosure, knowledge and products available in the art, and skill of the ordinary artisan allow such an artisan to practice the claimed methods without undue experimentation.

The Office Action noted the absence of any mention of a specialized sample holding structure, such as a capillary tube, in the rejected claims. The Office Action went on to assert that use of capillary tubes is critical to the invention and is lacking in the prior art. The assertion is based on a "factual basis", determined from the disclosure of Wittwer et al. (*Biotechniques* 10(1):76-83 (1991)) and Swerdlow et al. (*Biotechniques* 15(3):512-519 (1993)). Applicants submit that the present specification, as well as the specification of the priority documents, including the '029 application, are fully enabling for one of skill in the art to utilize any number of sample holders in the present methods. Furthermore, Applicants submit that the cited references do not provide the factual basis asserted, but rather, support a factual basis that capillary tubes are only an example of the type of sample holder useful in the present invention.

The Examiner is directed to the '029 application, as the present remarks also apply to the question of priority, discussed above. As discussed above, the '029 application states that the invention is directed to thermal cycling of sample containers through a predetermined temperature cycle. Capillary tubes are provided as an example of such sample containers.

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The '029 application teaches that automated nucleic acid amplification methods generally employ a plurality of tubular containers, the previously preferred container being plastic microcentrifuge tubes (page 2, lines 17-21). Thus, the use of various sample containers is well understood by the skilled artisan. And, the claim methods are clearly directed to such automation.

The '029 application also teaches throughout that the goal is to minimize thermal mass of all components associated with the device with which the present methods are used (e.g., page 8, lines 5-10; page 10, line 22 to page 11, line 3; page 13, line 26 to page 14, line 5). The skilled artisan would understand that this includes the sample holder.

The 029 application provides examples of useful containers such as "hollow elongate glass tubes" (page 14, lines 6-10). Capillary tubes are provided as a best mode, as is illustrated in the examples. The skilled artisan would understand that the choice of the capillary tube for use in the examples is as much a result of their abundant availability, low cost and widespread use in the field (i.e., familiarity) as their relatively low thermal mass and small volume (to hold a 10 μ l sample, *see* page 16, line 13). One of ordinary skill in the art at the time of the '029 application would be able to take the example on pages 16-17, along with the instruction of the specification, into consideration for a given application and determine a suitable sample holder, which may or may not be a capillary vessel.

The Office Action cites the disclosures of Wittwer et al. and Swerdlow et al. to conclude a factual basis to support the enablement rejection. The Office Action points to the discussion in Wittwer et al. (page 82, third column) about the shortcomings of the prior art devices. It is clear to even the casual reader that the slowness of the prior art devices for thermal cycling is a result of the type of thermal exchange system used (i.e., heat block or water bath) and type of material used for the sample holder (i.e., plastic centrifuge tube; *see* page 76, first paragraph of introduction). While thin capillary tubes are described as ideal, Wittwer et al. explains that the sample holder should be a symmetric, high surface area-to-volume container (page 78, middle column). The skilled artisan would see the shortcoming of the plastic centrifuge tube, which is generally conical in shape, which is the only container type that Wittwer et al. excludes. However, the skilled artisan would also see that many other containers beside capillary tubes would satisfy the needs for a specific

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application. The present methods employ heated fluids, and the '029 application describes that this innovation is the element that overcomes the limitations of the prior art, not the sample holder. This reference does not teach or suggest that capillary tubes are the only type of sample holder that can be used to accomplish the features of the present methods.

The Office Action also cites Swerdlow et al. for the conclusion that capillary vessels are "needed" for the rapid temperature changes of the present invention. as with Wittwer et al., the reference to capillary tubes only describes what has been used, not what can be used. The passage cited by the Examiner (paragraph bridging pages 512 and 513) emphasizes that the feature of the capillary tubes that make them functional is not the fact that they are capillary tubes but that they have low thermal mass. This is also the point emphasized in the '029 specification and all priority documents up to the present application. Furthermore, Swerdlow et al. emphasizes the difference between the improved method and the prior art as being the difference between air-based thermal cycling and block (i.e., heat block) thermal cycling.

The Office Action discusses that heat block and other prior art devices are not capable of changing temperature as rapidly as required in the rejected claims, citing the discussion on pages 78-80 of Wittwer et al. However, the rapid temperature changes achieved in the claimed methods are not a product of utilizing capillary tubes with otherwise known art. The use of capillary tubes is provided as a preferred embodiment, but the skilled artisan would readily recognize from the present and priority disclosures that any vessel chosen which takes into consideration low thermal mass, along with parameters already known in the art, can be used in the present invention. The claimed methods are made possible by the teachings of the specification as a whole. Determination of an appropriate sample holder, whether a capillary tube or some other sample container, can be easily made by the skilled artisan without undue experimentation.

Also, regardless of the means employed to obtain them, the present inventors are the first to show that reduction in denaturation and annealing times, as well as the rate of transition between the two, results in an improved method of amplifying a DNA sequence by thermal cycling. Likewise, methods for improving the purity of a product produced by PCR and for increasing the yield of an amplified DNA sequence have been shown for the

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first time by the Applicants. Applicants have provided means for performing such methods. However, the method steps are applicable and the improvement is obtained by following the prescribed steps, regardless of the apparatus used to obtain the time sequences. Therefore, Applicants submit that inclusion of the apparatus necessary to obtain the rapid temperature changes need not be an element of the claims. Applicants provide an example of how such temperature changes can be made, but, more importantly, they have shown the utility of such rapid changes.

In light of the discussion above, Applicants submit that the present claims satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102 and 103

Claims 30, 31, 33, 35, 37, 39-41, 43, 57 and 58 were rejected under 35 U.S.C. § 102(b) as being anticipated by Wittwer et al. The basis for this rejection was that the priority applications do not enable the present claims. As discussed above, the present claims are fully enabled by the '029 application, having a priority date of June 4, 1990. Therefore, the Wittwer et al. reference is not prior art as to the present claims.

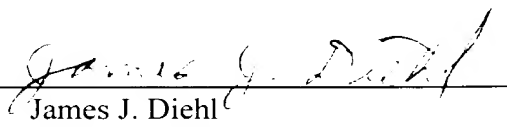
Claims 30-45, 57 and 58 were rejected under 35 U.S.C. § 102(b) as being anticipated by Swerdlow et al., *Biotechniques* 15(3): 512-519 (1993). In addition, Claims 30, 31, 33, 35, 37, 39-41, 43 and 45 57 and 58 were rejected under 35 U.S.C. § 103(a) as being obvious over Haff et al., USPN 5,827,480. As discussed above, the present claims are fully enabled by the '029 application. Swerdlow et al. was published in 1993. Haff has an earliest priority date of 1993. Therefore, these references are not prior art as to the present claims.

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On the basis of the amendments and remarks presented herein, Applicants believe that this application is now in condition for immediate allowance. Applicants respectfully request that the Examiner pass this application to issue, and early notice of such is requested.

Respectfully submitted,
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